N-Acetyltransferase polymorphisms and colorectal cancer: a review

Tables 1 - 5

Table 1. Human NAT2 allele designations (after Vatsis et al., 1995 (5), updated by personal communication, 1998)

Allele	Substitution*									
	$C^{481}T$	$C^{282}T$	$C^{759}T$	$G^{191}A$	$T^{341}C$	$A^{434}C$	$G^{590}A$	$A^{803}G$	$G^{845}C$	$G^{857}A$
***NAT2**4 (wildtype)**										
***NAT2**5A**	●				●					
***NAT2**5B**	●				●			●		
***NAT2**5C**					●			●		
***NAT2**5D**					●					
***NAT2**5E**					●		●			
***NAT2**5F**	●		●		●			●		
***NAT2**6A**		●					●			
***NAT2**6B**							●			
***NAT2**6C**		●					●	●		
***NAT2**7A**										●
***NAT2**7B**		●								●
***NAT2**12A**								●		
***NAT2**12B**		●						●		
***NAT2**12C**	●							●		
***NAT2**13**		●								
***NAT2**14A**				●						
***NAT2**14B**		●		●						
***NAT2**14C**	●			●	●			●		
***NAT2**14D**		●		●			●			
***NAT2**14E**				●				●		
***NAT2**14F**		●		●				●		
***NAT2**17**	●				●	●		●		

***NAT2**18**	●

* C, cytosine; T, thymine; G, guanine; A, adenine.

Table 2. Functional significance of *NAT2* mutations

Substitution*	Amino acid sequence change†	Observed in combination with one or more of :	Correlation with phenotype⋆	Reference
$C^{481}T$	Silent	$T^{341}C$, $A^{803}G$, $C^{759}T$, $G^{191}A$, $A^{434}C$	No change alone but necessary for $T^{341}C$ to affect activity	Blum et al., 1991 (12)
$C^{282}T$	Silent	$G^{590}A$, $A^{803}G$, $G^{857}A$, $C^{282}T$, $G^{191}A$	No change	Blum et al., 1991 (12)
$C^{759}T$	Silent	$C^{481}T$, $T^{341}C$, $A^{803}G$	No change	Woolhouse et al., 1997 (15)
$G^{191}A$	$Arg^{64}Gln$	$C^{282}T$, $C^{481}T$, $T^{341}C$, $A^{803}G$, $G^{590}A$	Reduced enzyme activity, highly conserved region of the active site for acetyl transfer	Bell et al., 1993 (16); Deloménie et al., 1996 (17)
$T^{341}C$	$Ile^{114}Thr$	$C^{481}T$, $A^{803}G$, $G^{590}A$, $C^{759}T$, $G^{191}A$, $A^{434}C$	Reduces enzyme activity if combined with $C^{481}T$	Blum et al., 1991 (12)
$A^{434}C$	$Gln^{145}Pro$	$T^{341}C$, $C^{481}T$, $A^{803}G$	Unknown	Lin et al., 1994 (18)
$G^{590}A$	$Arg^{197}Gln$	$C^{282}T$, $T^{341}C$, $A^{803}G$, $G^{191}A$	Reduces half-life of protein (from 22 to 6 hours); affinity unchanged	Blum et al., 1991 (12)
$A^{803}G$	$Lys^{268}Arg$	$G^{191}A$, $C^{282}T$, $T^{341}C$, $C^{481}T$, $C^{759}T$, $A^{434}C$	No change if alone	Cascorbi et al., 1996 (19)
$G^{845}C$	$Lys^{282}Thr$	None	Unknown	Lin et al., 1994 (18)
$G^{857}A$	$Gly^{286}Arg$	$C^{282}T$	Decreased activity	Ohsako and Deguchi, 1990 (13)

***** C, cytosine; T, thymine; G, guanine; A, adenin; Arg, arginine; Gln, glutamine; Ile, isoleucine; Thr, threonine; Pro, proline; Lys, lysine; Gly, glycine.

† Information given in this column suggests the likely effect of the given mutation if present alone. However, this effect may be modified by the presence of other mutations.

Table 3. Frequency of predicted *NAT2* acetylator status in different groups of subjects

a) Studies based on NAT2 genotyping

Area of study	Subjects	Frequency of fast acetylators (%) (95% CI)	Frequency of intermediate acetylators (%) (95% CI)	Frequency of fast or intermediate acetylators (%) (95% CI)	Reference
Africa					
Gabon	52 subjects	0 (0-6.8)	12 (4.4-23.4)	12 (4.4-23.4)	Deloménie et al., 1996 (27)
Mali	50 non-caste Dogon subjects	4 (0.4-13.7)	18 (8.6-31.4)	22 (11.5-40.0)	Deloménie et al., 1996 (27)
Americas					
Nicaragua, León	137 University students and staff of Central American Indian-white mixed origin (Mean age (SD) 24.5 years ±7; 42% ♂)	22 (15.3-29.8)	28 (21.1-36.8)	50 (41.7-59.0)	Martinez et al., 1998 (28)
USA, Boston	466 white ♀ matched to cases of breast cancer within Nurses' Health Study			42 (37.7-46.9)	Hunter et al., 1997 (29)
USA, Los Angeles	98 United States, Koreans	46 (35.8-56.3)	41 (31.0-51.2)	87 (78.4-92.7)	Lin et al., 1993 (14)
	96 United States, Black	19 (11.5-28.0)	44 (33.6-54.3)	63 (52.0-72.2)	
	83 United States, Hispanic-Harbour	19 (11.4-29.4)	47 (35.9-58.3)	66 (55.0-76.3)	
	65 United States, Hispanic-UCLA	8 (2.5-17.0)	63 (50.2-74.7)	71 (58.2-81.4)	
	99 United States, Jewish	6 (2.3-12.7)	32 (23.3-42.5)	38 (28.8-48.7)	
	76 United States, white	5 (1.4-12.9)	42 (30.9-54.0)	47 (35.8-59.2)	
	99 United States, mixed	13 (7.2-21.4)	35 (26.0-45.6)	48 (38.3-58.7)	
USA, Los Angeles	61 Asian Indians	7 (1.8-15.9)	39 (27.1-52.7)	46 (33.1-59.2)	Lin et al., 1994 (18)
	79 Japanese	42 (30.8-53.4)	44 (33.1-55.9)	86 (76.4-92.8)	
	100 Filipino	16 (9.4-24.7)	47 (36.9-57.2)	63 (52.8-72.4)	

Area of study	Subjects	Frequency of fast acetylators (%) (95% CI)	Frequency of intermediate acetylators (%) (95% CI)	Frequency of fast or intermediate acetylators (%) (95% CI)	Reference
USA, Los Angeles	484 subjects undergoing sigmoidoscopy; no history of polyps (67.4% ♂; 54.8% white)			47 (42.2-51.3)	Probst-Hensch et al., 1996 (30)
USA, Minnesota	633 individuals undergoing colonoscopy at private clinics and found to be polyp free (age 30-74 years 39% ♂)	7 (4.8 – 8.9)	35 (30.7-38.3)	41 (37.2-45.0)	Potter et al., 1999 (31)
USA, New York	114 Pre-menopausal white ♀ 213 Post-menopausal white ♀	8 (3.7-14.5) 8 (4.7-12.5)	35 (26.4-44.6) 39 (32.4-45.9)	43 (33.7-52.6) 47 (40.1-53.9)	Ambrosone et al., 1996 (32)
USA, New York	179 ♀ whites with 2 or more live births			48 (40.5-55.6)	Mendola et al., 1998 (33)
USA, North Carolina	500 subjects; 255 community based volunteers, 203 urology clinic patients and 42 white subjects from Georgia, USA White (n=372) African-Americans (n=128)	 6 (4.0-9.1) 14 (8.6-21.3)	 38 (33.2-43.3) 45 (35.7-53.6)	 44 (39.2-49.6) 59 (49.6-67.2)	Bell et al., 1993 (16)
USA, North Carolina	29 ♀ with at least 2 previous live births Black (n=7) White (n=22)			 57 (18.4-90.1) 36 (17.1-59.3)	Hirvonen et al., 1996 (34)
USA, North Carolina	473 ♀ from Motor Vehicle Registry and Health Care Financing Administration (age range 20-74). African Americans (n=198) White (n=275)	 13 (8.8-18.6) 6 (3.6-9.7)	 47 (39.9-54.2) 34 (28.5-40.0)	 60 (52.9-70.0) 40 (34.1-46.0)	Millikan et al., 1998 (35)
USA, Texas	90 subjects matched to glioma patients (58%♂; 87% non-Hispanic white, 13% African-American, 4% Hispanic)			67 (55.9-76.3)	Trizna et al., 1998 (36)

Area of study	Subjects	Frequency of fast acetylators (%) (95% CI)	Frequency of intermediate acetylators (%) (95% CI)	Frequency of fast or intermediate acetylators (%) (95% CI)	Reference
USA, Utah	1033 ♂ and 922 ♀ subjects (91% non-Hispanic whites)				Slattery et al., 1998 (37)
	♂	7 (5.5-8.7)	35 (31.8-37.7)	42 (38.7-44.8)	
	♀	6 (4.2-7.3)	35 (31.6-37.9)	40 (37.2-43.6)	
USA	221 white ♂ from the Physicians' Health Study			43 (36.8-50.3)	Chen et al., 1998 (38)
Asia					
Hong Kong	70 Chinese subjects	23 (13.7-34.4)	50 (37.8-62.2)	73 (60.9-82.8)	Lin et al., 1993 (14)
India, Ahmedabad	31 ♂ factory workers (Mean age (SD) 25 years ±4.5)			32 (16.7-51.4)	Rothman et al., 1997 (39)
Japan, Fukuoko	329 healthy volunteers	45 (39.2-50.2)	46 (40.4-51.4)	91 (86.9-93.5)	Shibuta et al., 1994 (40); Asada et al., 1997 (41)
Japan, Kitakyushu	122 subjects from 3 general health clinics (Mean age (SD) 62.4 years ±16.5; 41% ♂)	50 (40.8-59.2)	44 (35.3-53.5)	94 (88.5-97.7)	Katoh et al., 1998 (42)
Japan, Kobe	120 healthy volunteers and 25 hospitalised patients (age range 20-78 years; 27% ♂)	44 (35.9-52.6)	49 (40.6-57.4)	93 (87.7-96.6)	Okumura et al., 1997 (43)
Japan, Northern Kyushu	376 healthy factory workers (91% ♂; median age 36 years, range 20-71)	50 (45.1-55.4)	39 (34.1-44.2)	89 (85.8-92.3)	Oyama et al., 1997 (44)
Japan	164 subjects without history of malignancy undergoing health check-ups (Mean age (SD) 49.8 years ±9.7, range 29-74; 62% ♂)	57 (49.4-65.0)	32 (25.2-40.1)	90 (83.9-93.8)	Morita et al., 1998 (45)
Malaysia	146 unrelated university students and staff (Malay; age range 18-55 years; 52% ♂)	25 (17.9-32.5)	33 (25.3-41.1)	58 (49.1-65.7)	Zhao et al., 1995 (46)
	139 university students and staff (Indian; age range 19-57 years; 62% ♂)	25 (18.2-33.2)	37 (28.7-45.3)	62 (53.3-70.0)	

Area of study	Subjects	Frequency of fast acetylators (%) (95% CI)	Frequency of intermediate acetylators (%) (95% CI)	Frequency of fast or intermediate acetylators (%) (95% CI)	Reference
Singapore	187 healthy undergraduates	29 (23.0-36.5)	42 (35.1-49.7)	72 (64.6-78.0)	Lee et al., 1998 (47)
Taiwan	100 Taiwanese subjects	26 (17.7-35.7)	51 (40.8-61.1)	77 (67.5-84.8)	Lin et al., 1994 (18)
Turkey	303 unrelated outpatients with non-malignant conditions (Mean age 36 years, range 8-90; 62% ♂)	4 (2.1-6.8)	39 (33.1-44.4)	43 (36.9-48.4)	Aynacioglu et al., 1997 (48)
United Arab Emirates	106 healthy unrelated schoolboys, aged 12-17 years	2 (0.2-6.6)	35 (25.9-44.8)	37 (27.6-46.7)	Woolhouse et al., 1997 (49)
Europe					
Denmark, Aarhus	90 healthy, white, non-smoking bus drivers (Mean age 45 years; 72% ♂)			49 (38.2-59.7)	Nielsen et al., 1996 (50)
Denmark	242 subjects of Danish ethnic background, with non-cancerous diseases of the urinary tract not associated with smoking (Mean age (SD) 64 years ±12; 51% ♂)	7 (3.8-10.5)	38 (31.5-44.0)	44 (37.9-50.7)	Okkels et al., 1997 (51)
France	88 samples from Centre d'etude du Polymorphisme Humain cell bank (age range 20-70 years)	0 (0-4.1)	13 (6.4-21.3)	13 (6.4-21.3)	Muiras et al., 1998 (52)
France	119 healthy unrelated white subjects (Mean age (SD) 55 years ±12)			39 (29.9-48.0)	Bendriss et al., 1998 (53)
France	172 regular smokers without previous or current malignancy, from 10 hospitals	6 (2.8-10.4)	41 (33.8-49.0)	47 (39.5-54.8)	Bouchardy et al., 1998 (54)
Germany, Berlin	844 subjects	4 (3.0-5.9)	37 (33.6-40.2)	41 (37.8-44.5)	Cascorbi et al., 1995 (55)
Germany, Bremen	154 unrelated healthy subjects; (57% ♂, mean age (SD) 38.2 years ±12.6, range 17-65); 43% ♀ (Mean age (SD) 36.1 years ±13, range 22-76)	6 (3.2-11.6)	39 (31.2-47.1)	45 (37.4-53.7)	Schnakenberg et al., 1998 (56)

Area of study	Subjects	Frequency of fast acetylators (%) (95% CI)	Frequency of intermediate acetylators (%) (95% CI)	Frequency of fast or intermediate acetylators (%) (95% CI)	Reference
Germany	100 white subjects from community groups via UCLA Tissue Typing Laboratory	8 (3.5-15.2)	32 (23.0-42.1)	40 (30.3-50.3)	Lin et al., 1993 (14)
Germany	310 hospitalised subjects with non-malignant conditions matched to lung cancer patients	5 (2.7-7.9)	37 (31.4-42.4)	42 (36.1-47.3)	Cascorbi et al., 1996 (57)
	278 healthy volunteers	5 (2.8-8.3)	37 (31.0-42.7)	42 (35.9-47.8)	
Germany	373 inpatients of German extraction without malignant disease from 3 hospitals (Mean age 65.8 years; 35.3% ♂)	4 (2.5-6.9)	38 (33.1-43.2)	42 (37.3-47.6)	Brockmöller et al., 1996 (58)
Germany	78 subjects; 48 hospitalised cancer free patients, 29 healthy volunteer blood donors from Italy and France and 1 unspecified			42 (31.2-54.0)	Bartsch et al., 1998 (59)
Italy	44 healthy non-smoking volunteers (31.8% ♂)			36 (22.4-52.2)	Gabbani et al., 1998 (60)
Netherlands	35 smokers and 4 non-smokers (only 35 genotyped)			40 (23.9-57.9)	Dallinga et al., 1998 (61)
Poland, Lodz	100 hospitalised children with normal postnatal development (Mean age (SD) 1.5 years ±3.0; 62% ♂)	8 (3.5-15.2)	38 (28.5-48.3)	46 (36.0-56.3)	Zielinska et al., 1997 (62)
Poland	248 children of Polish origin with respiratory or urinary infection	7 (4.0-10.7)	30 (24.6-36.4)	37 (31.1-43.4)	Mrozikiewicz et al., 1996 (63)
Poland	20 hospitalised children (age range 2-12 months, mean 6.35 months; 50% ♂)			35 (15.4-59.2)	Zielinska et al., 1998 (64)
Portugal, Coimbra	128 unrelated hospital and faculty staff and students	6 (2.7-11.9)	30 (21.9-38.4)	36 (27.7-44.9)	Lemos et al., 1998 (65)
Portugal	201 subjects recruited at medical check-ups (Mean age (SD) 46 years ±19.6)	6 (3.5-10.8)	34 (27.3-40.8)	40 (33.5-47.4)	Gil et al., 1998 (66)

Area of study	Subjects	Frequency of fast acetylators (%) (95% CI)	Frequency of intermediate acetylators (%) (95% CI)	Frequency of fast or intermediate acetylators (%) (95% CI)	Reference
Slovak Republic, Kosice	64 ♂ coke oven workers 34 ♂ machine workers			45 (32.8-58.3) 26 (12.9-44.4)	Kalina et al., 1998 (67)
Slovak Republic, Kosice	68 coke oven workers 59 machine workers			47 (34.8-59.6) 27 (16.4-40.3)	Binková et al., 1998 (68)
Spain	132 ♀ healthy subjects (age range 19-81 years)	14 (8.3-20.7)	36 (27.5-44.4)	49 (40.4-58.1)	Agúndez et al., 1995 (69)
Spain	243 unrelated white subjects (43.6% ♂)	7 (4.1-11.0)	35 (28.6-40.9)	42 (35.3-48.0)	Martinez et al., 1995 (70)
Spain	258 unrelated white subjects (Mean age (SD) 45.4 years ±12.9, range 18-95; 45% ♂)	7 (3.8-10.3)	38 (32.4-44.6)	45 (38.8-51.3)	Agúndez et al., 1996 (71)
Spain	217 healthy white medical students and teachers (Mean age 36.5 years, range 20-48; 46% ♂)	7 (3.9-11.1)	39 (32.6-46.0)	46 (39.3-53.0)	Agúndez et al., 1996 (72)
Spain	217 healthy white subjects (Mean age (SD) 36.3 years ±12.7; 59% ♂)	8 (4.6-12.2)	38 (31.8-45.1)	46 (39.3-53.0)	Agúndez et al., 1997 (73)
Spain	160 healthy university staff and students	9 (4.9-14.2)	39 (31.8-47.4)	48 (40.2-56.2)	Agúndez et al., 1998 (74)
Spain	121 white hospital staff and university staff and students	7 (2.9-12.6)	38 (29.3-47.3)	45 (35.6-53.9)	Agúndez et al., 1998 (75)
Sweden	30 ♂ pipelayers (Median age 43.5 years, range 19-60)	20 (7.7-38.6)	43 (25.5-62.6)	63 (43.9-80.1)	Dalene et al., 1996 (76)
Sweden	70 healthy white volunteers	9 (3.2-17.7)	21 (12.5-32.9)	30 (19.6-42.1)	Smith et al., 1997 (21)
Sweden	164 subjects aged ≥30 years from Stockholm County population register (28.7% ♂)			39 (31.5-46.9)	Nyberg et al., 1998 (77)
UK, Dundee	96 white subjects	5 (1.7-11.7)	30 (21.3-40.4)	35 (25.9-45.8)	Smith et al., 1997 (21)

Area of study	Subjects	Frequency of fast acetylators (%) (95% CI)	Frequency of intermediate acetylators (%) (95% CI)	Frequency of fast or intermediate acetylators (%) (95% CI)	Reference
UK, Edinburgh	343 white subjects visiting occupational screening clinic	7 (4.8-10.6)	34 (28.5-38.8)	41 (35.6-46.2)	Hubbard et al., 1997 (78)
UK, London	100 deceased subjects, >60 years (Mean age (SD) 77.1 years ±8.8; 65% ♂)			63 (52.8-72.4)	Bandmann et al., 1997 (79)
UK, Oxford	19 healthy white volunteers (age range 18-32 years) (only 17 genotyped)	6 (0.1-28.7)	18 (3.8-43.4)	24 (6.8-49.9)	Risch et al., 1996 (80)
UK, Newcastle	174 subjects recruited from general practitioner patient lists and matched to colorectal cancer cases (99% white)			42 (34.5-49.7)	Welfare et al., 1997 (81)
UK, Staffordshire	112 patients hospitalised for non-cancer conditions			45 (35.2-54.3)	Bell et al., 1995 (25)
Oceania					
New Zealand	25 subjects of Samoan ethnic group	52 (31.3-72.2)	16 (4.5-36.1)	68 (46.5-85.1)	Lin et al., 1994 (18)

b) Studies based on phenotyping

Area of study	Subjects	Frequency of fast acetylators (%) (95% CI)	Frequency of intermediate acetylators (%) (95% CI)	Frequency of fast or intermediate acetylators (%) (95% CI)	Reference
Africa					
Republic of South Africa	60 subjects of mixed ethnic group with previously untreated tuberculosis (Mean age (SD) 34 years ±10, range 18-60; 72% ♂)	20 (10.8-32.3)	45 (32.1-58.4)	65 (51.6-76.9)	Parkin et al., 1997 (82)
Americas					
USA, Arkansas	41 surgical patients undergoing surgery for diseases other than cancer			27 (14.2-42.9)	Lang et al., 1986 (7)
USA, North Dakota	12 patients without cancer	17 (2.1-48.4)	58 (27.7-84.8)	75 (42.8-94.5)	Kirlin et al., 1991 (83)
Asia					
India	30 from benzidine handling subjects factories and 18 building construction workers			31 (18.7-46.3)	Rothman et al., 1996 (84)
Japan, Akita	297 ♂ Japanese hydrazine workers from 3 districts (Mean age (SD) 41.4 years ±11.9)	45 (39.0-50.6)	45 (39.4-51.0)	90 (85.9-93.1)	Koizumi et al., 1998 (85)
	Shikoku district (n=178)	48 (40.8-55.9)	43 (35.3-50.3)	91 (85.8-94.8)	
	Kinki district (n=44)	32 (18.6-47.6)	59 (43.3-73.7)	91 (78.3-97.5)	
	Hokuriku district (n=75)	44 (32.5-55.9)	43 (31.3-54.6)	87 (76.8-93.4)	
Russia, Leningrad	38 ♀ subjects (some with age-related cardiovascular disturbances)			37 (21.8-54.0)	Bulovskaya et al., 1978 (86)
Turkey	51 ♂ healthy volunteers of Turkish ancestry (age range 26-61 years)			35 (22.4-49.9)	Sardas et al., 1990 (87)

Area of study	Subjects	Frequency of fast acetylators (%) (95% CI)	Frequency of intermediate acetylators (%) (95% CI)	Frequency of fast or intermediate acetylators (%) (95% CI)	Reference
Europe					
Germany, Gottingen	85 local healthcare employees without contact allergies or atopic disease			24 (15.0-34.0)	Schnuch et al., 1998 (88)
Spain, Madrid	75 ♀ subjects			40 (28.9-52.0)	Ladero et al., 1987 (89)
Spain, Madrid	96 healthy subjects (Mean age (SD) 63.4 years ±8.4; 42 ♂)			42 (31.7-52.2)	Ladero et al., 1991 (90)
UK, Cardiff	100 ♀ subjects; 32 with benign breast lumps and 68 healthy drug-free volunteers from local factory			41 (31.3-51.3)	Webster et al., 1989 (91)
UK, Huddersfield & London	95 Huddersfield residents 112 London residents			45 (35.0-55.8) 38 (29.4-48.1)	Cartwright et al., 1982 (92)
UK, London	337 white British staff and others at medical school and hospital			44 (38.5-49.4)	Philip et al., 1987 (93)
Oceania					
Australia, Western	20 convalescent patients and 28 healthy volunteers; (Mean age 61 years, range 38-89)			35 (22.2-50.5)	Ilett et al., 1990 (94)

c) Studies based on NAT1 genotyping

Area of Study	Subjects	Frequency of wild-type homozygotes (% (95% CI))	Alleles detected	Reference
Americas				
USA, Los Angeles	484 subjects undergoing sigmoidoscopy; no history of polyps (67.4% ♂; 54.8% white)	50 (45.5-54.5)	NAT1*3 NAT1*4 NAT1*10	Probst-Hensch et al., 1996 (30)
USA, North Carolina	473♀ from Motor Vehicle Registry and Health Care Financing Administration (age range 20-74) African-Americans (n=198) Whites (n=275)	 24 (11.3-30.7) 62 (55.9-67.7)	NAT1*3 NAT1*4 NAT1*10 NAT1*11	Millikan et al., 1998 (35)
USA	221 white ♂ from the Physicians' Health Study	44 (37.7-51.2)	NAT1*3 NAT1*4 NAT1*10 NAT1*11	Chen et al., 1998 (38)
Asia				
Japan	122 subjects from 3 general health clinics (Mean age (SD) 62.4 years ±16.5; 41% ♂)	38 (29.1-46.9)	NAT1*3 NAT1*4 NAT1*10 NAT1*11 NAT1*14 NAT1*15 NAT1*17	Katoh et al., 1998 (42)
Europe				
Denmark	242 subjects of Danish ethnic background with non-cancerous disease of the urinary tract not associated with smoking (Mean age (SD) 64 years ±12; 51% ♂)	48 (41.1-54.0)	NAT1*4 NAT1*10 NAT1*11	Okkels et al., 1997 (51)

Area of Study	Subjects	Frequency of wild-type homozygotes (% (95% CI))	Alleles detected	Reference
France	172 regular smokers without previous or current cancer from 10 hospitals (9 in Paris)	55 (47.5-62.8)	NAT1*3 NAT1*4 NAT1*10 NAT1*11 NAT1*14 NAT1*15	Bouchardy et al., 1998 (54)
UK, Edinburgh	323 white subjects visiting occupational screening clinic	96 (93.6-98.1)	NAT1*4 NAT1*14 NAT1*15	Hubbard et al., 1998 (95)
UK, Staffordshire	112 patients hospitalised for non-cancer conditions	29 (21.2-38.8)	NAT1*3 NAT1*4 NAT1*10 NAT1*11	Bell et al., 1995 (25)
Oceania				
Australia, Perth	85 subjects primarily of European origin	92 (83.8-96.6)	Not stated	Butcher et al., 1997 (23)

Table 4. Summary of studies of colorectal neoplasia and acetylator phenotype

a) NAT2 -specific phenotype

Area of study	Cases		Controls		RR (95% CI) for fast and intermediate acetylators *vs.* slow acetylators	Exposure assessment	Reference
	Type	No.	Type	No.			
Australia, West	Patients who had undergone surgical resection for *colorectal adenocarcinoma*; 71% male	49	Patients and volunteers of similar age, sex and ethnicity as cases; without cancer; 80% male	41	3.8 (1.5-9.3)	Smoking and alcohol assessed; not analysed with acetylator status.	Ilett et al., 1987 (119)
Australia, South	Cases with *colorectal cancer* from 1 hospital; 55% enrolled prospectively, 45% with resection within preceeding two years; whites, median age 69 years	110	Subjects who had undergone colonoscopy or barium enema in same hospital as cases who had no neoplastic lesions: whites, median age 69 years	110	1.8 (1.0-3.3)	Meat consumption assessed. Analysed with phenotype.	Roberts-Thomson et al., 1996 (120)
	Subjects who had undergone colonoscopy or barium enema in the same hospital as cancer cases who had histologically confirmed *colorectal adenomas*, whites, median age 69 years, male:female ratio 2:1	89	Same control group as above		1.1 (0.6-2.1)		
Spain	Cases of histologically diagnosed *colorectal cancer*; 48% male	109	"Healthy" subjects; source not stated; 44% male	96	1.1 (0.7-2.0)	None	Ladero et al., 1991 (90)
USA, Arkansas	Male hospital patients with a history of *colorectal cancer*	43	Male hospital patients without malignant disease	41	2.5 (1.0-6.4)	Diet, smoking, exercise, medical history and occupational history assessed. Analysed with phenotype.	Lang et al., 1986 (7); Wohleb et al., 1990 (118)

b) Non-specific Acetylator Phenotype

Area of study	Cases		Controls		RR (95% CI) for fast and intermediate acetylators	Exposure assessment	Reference
	Type	No.	Type	No.	*vs.* slow acetylators		
USA, Arkansas	Subjects with *colon cancer* (n=34) or *colon polyps* (n=41) admitted to one hospital; 56% male; mean age 60 years	75	Subjects selected by random digit dialling in central Arkansas; 63% male; mean age 47 years	205	1.3 (0.8-2.3)	Diet, meat cooking preference and smoking status assessed. Analysed with *NAT2* and CYP1A2 phenotypes combined.	Lang et al., 1994 (121)

Table 5. Summary of studies of colorectal neoplasia and NAT1 and *NAT2* genotype

Area of Study	Cases		Controls		*NAT2*	NAT1			Exposure Assessment	Reference
	Type	N	Type	N	RR (95% CI) for fast and intermediate acetylators vs slow acetylators	Alleles investigated	Genotype comparison	RR (95% CI)		
Japan	Cases of histologically confirmed *colorectal cancer*. 53% ♂	234	"Healthy" volunteers	329	0.8 (0.5-1.4)				None	Shibuta et al., 1994 (40)
Japan	Colon tissue samples, from *colorectal cancer* cases, obtained at surgery in 3 hospitals in Kanazawa. Mean age 67.2 years, range 38-81; 44% ♂	36	Liver autopsy samples age matched to cases	36	1.0 (0.2-4.7)				None	Oda et al., 1994 (122)
Portugal, Lisbon	Unrelated *colorectal cancer* patients from Lisbon area. Mean age (SD) 64.2 years ±11; 63% ♂	114	Recruited from medical check-ups. Mean age (SD) 46 years ±19.6	201	2.0 (1.3-3.2)				None	Gil et al., 1998 (66)
Singapore	Chinese *colorectal cancer* patients recruited from surgical departments of two hospitals. Mean age 47 years; 59% ♂	216[☞]	"Healthy" undergraduates and blood donors; mean age 27 years; 73% ♂	187	1.1 (0.7-1.7)	*NAT1**3 *NAT1**4 *NAT1**10 *NAT1**11	Not stated	1.0[†]	None	Lee et al., 1998 (125)
UK, Lothian	Consecutive series of operable patients with *colorectal cancer* from 4 hospitals	275	"Healthy" individuals attending occupational screening clinics	343	0.8 (0.6-1.2)				None	Hubbard et al., 1997 (78)
UK, Newcastle and North Tyneside	Population based cases of *colorectal cancer*, source not stated. Median age 69 years, 59% ♂	174	Population-based controls selected from primary care registers, matched with cases on age, sex and general practitioner	174	1.0 (0.6-1.5)				Diet assessed by food frequency questionnaire. Smoking status and alcohol intake assessed. Exposure analysed with genotype.	Welfare et al., 1997 (81)

Area of Study	Cases		Controls		*NAT2*	NAT1			Exposure Assessment	Reference
	Type	N	Type	N	RR (95% CI) for fast and intermediate acetylators vs slow acetylators	Alleles investigated	Genotype comparison	RR (95% CI)		
UK, North Staffordshire	Sample of incident cases of *colorectal adenocarcinoma* from 1 hospital	202	Hospitalised patients undergoing treatment for non-cancerous conditions	112	1.1 (0.7-1.8)	*NAT1**3 *NAT1**4 *NAT1**10 *NAT1**11	Heterozygous/ homozygous *NAT1**10 *vs* all others	1.9 (1.2-3.1)	Smoking status available for cases only; analysed with genotype	Bell et al., 1995 (25)
UK, Scotland	Consecutive series of operable patients with *colorectal cancer* from 3 hospitals	260	"Healthy" individuals attending occupational screening clinics	323		*NAT1**4 *NAT1**14 *NAT1**15	*NAT1**4/*15 or *NAT1**4/*14 genotypes *vs* *NAT1**4/*4 genotype	1.0[†]	None	Hubbard et al., 1998 (95)
USA	*Colorectal cancer* samples obtained from Disease Research Interchange and Co-operative Human Tissue Network. Mean age 62 years; 61% ♂; 72% white	44	Non-cancer colon samples from same sources as cases. Mean age 53 years; 21% ♂; 75% white	28	1.0 (0.4-2.5)				None	Rodriguez et al., 1993 (8)
USA, Los Angeles County, California	Subjects who had undergone sigmoidoscopy where a *colorectal adenoma* was found. 64% ♂; 55% white, 16% black, 17% Hispanic, 10% Asian	447[‡]	Subjects who had undergone sigmoidoscopy and had no current or past polyp; similar age, sex, ethnic distribution to cases	487[‡]	1.1 (0.8-1.4)	*NAT1**10	Heterozygous/ homozygous *NAT1**10 *vs* all others All cases Incident cases[§]	 1.1 (0.8-1.4) 2.3 (1.2-4.2)	Smoking status assessed and analysed with genotype	Probst-Hensch et al., 1995 (124); Probst-Hensch et al., 1996 (30)
USA, Los Angeles and Orange County, California	Subjects who had undergone sigmoidoscopy where a *colorectal adenoma* was found; 50-74 years	528	Subjects who had undergone sigmoidoscopy and had no current or past polyps, individually matched to cases	565	-[‖]	*NAT1**11 *NAT1**14 *NAT1**15 *NAT1**17 *NAT1**19 *NAT1**20 *NAT1**21 *NAT1**22 *NAT1**23 *NAT1**25	Low activity *NAT1* mutation (*14, *15, *17, *19 or *22) *vs* all other alleles combined	0.8 (0.4-1.5)	Smoking, exercise, diet, family history assessed by questionnaire. Not analysed with genotype	Lin et al., 1998 (24)[¶]

Area of Study	Cases		Controls		*NAT2*	NAT1			Exposure Assessment	Reference
	Type	N	Type	N	RR (95% CI) for fast and intermediate acetylators vs slow acetylators	Alleles investigated	Genotype comparison	RR (95% CI)		
USA, Minnesota	Individuals undergoing colonoscopy at private gastroenterology practices and found to have - at least one *adenoma* - at least one *hyperplastic polyp* and no adenomas	 527 200	Individuals undergoing colonoscopy at private gastroenterology practices and found to be polyp free	633	 1.1 (0.9-1.4)[#] 1.1 (0.8-1.6)[#]				Smoking status, pack years of smoking; analysed with genotype	Potter et al., 1999 (31)
USA, Utah[⊗]	Population-based cases of *colorectal cancer*; source not stated	1306[▽]	Population-based controls; source not stated	1533[▽]	1.0[Φ]	Not stated	Not stated	1.2 (0.8-1.8)	None	Jenkins et al., 1997 (123)
USA, Utah	Cases of primary *colon cancer* only; those with rectal cancer, known familial adenomatous polyposis, ulcerative colitis or Crohn's disease were excluded	1611	Controls randomly selected to meet age and sex distribution of cases from medical care program lists, drivers license lists, social security lists and random digit dialling	1955	1.1 (0.9-1.2)[♣]				Various measures of smoking and meat consumption assessed[=]; analysed with genotype	Slattery et al., 1998 (37); Kampmann et al., 1999 (126)
USA, multicentre	Male cases with *colorectal cancer* in Physicians' Health Study cohort, ascertained from questionnaires, with confirmation from medical records and the National Death Index	212	Controls selected from same cohort who had not developed cancer at the time the case was diagnosed	221	0.8 (0.5-1.3)	*NAT1**3 *NAT1**4 *NAT1**10 *NAT1**11	Heterozygous/ homozygous *NAT1**10 *vs* all others	0.9 (0.6-1.5)	Meat intake assessed by food frequency questionnaire; analysed with genotype	Chen et al., 1998 (38)

[☞] 68 cases were included in the analysis of *NAT1*.

[†] The authors stated that no significant differences in the frequencies of *NAT1* alleles between cases and controls were observed.

[‡] 441 cases and 484 controls were included in the analysis of *NAT1*.

[§] Negative sigmoidoscopy within previous 5 years.

[||] No relative risk reported. The authors state that there was no increased frequency of adenomas among subjects with *NAT2* fast acetylator genotype.

[¶] This study includes the subjects reported by Probst-Hensch et al. (30, 124).

[#] Crude relative risks. The authors present relative risks for (i) adenomas, fast *vs* slow 1.1 95% CI (0.6-1.9); (ii) adenomas, intermediate *vs* slow 1.195%CI (0.8-1.4); (iii) hyperplastic polyps, fast *vs* slow 0.9 95%CI (0.4-1.9) and (iv) hyperplastic polyps, intermediate *vs* slow 1.2 95%CI (0.8-1.6), adjusted for age, sex, NSAID drug use, hormone therapy drug use and smoking.

[⊗] Reported as an abstract only.

[▽] 146 cases and 183 controls were included in the analysis of NAT1.

[Φ] 95% CI could not be computed.

[♣] Crude relative risk. Slattery et al. (37) presented relative risks for men and women separately, adjusted for age, energy intake, body mass index, long term physical activity, dietary fibre and usual number of cigarettes smoked per day. Men RR=0.9 (0.6-1.2); women RR=1.0 (0.7-1.6).

[=] Slattery et al. (37) includes data on smoking; Kampmann et al. (126) includes data on meat consumption.